

In the Claims:

Please cancel claims 2, 3, 11, 18-20, 22, 39, and 40.

Please amend claims 1, 4-10, 12-17, 21, 24, 25, 27-31, 33-35, 38, and 41.

Please add new claims 42-49.

1. **(Currently amended)** ~~A~~ ~~An isolated and~~ recombinant fusion peptabody, which binds to an ~~the~~ epidermal growth factor receptor selected from the group consisting of ErbB-1, ErbB-3, and ~~or~~ ErbB-4, comprising:

- (a) a portion of a ~~humanized~~ cartilage oligomer matrix polypeptide;
- (b) ~~an~~ a peptide enhancer sequence for increasing protein production located at the N terminus of the portion of the ~~humanized~~ cartilage oligomer matrix polypeptide;
- (c) a portion of a hinge region of an immunoglobulin polypeptide located at the C terminus of the portion of the ~~humanized~~ cartilage oligomer matrix polypeptide; and
- (d) an epidermal growth factor receptor ligand located at the C terminus of the hinge region, ~~comprising at least a motif having a three-dimensional structure,~~

~~and whereby~~ wherein said ~~isolated and~~ recombinant fusion peptabody is capable of inducing cellular death in a cell expressing said epidermal growth factor receptor.

2. **(Canceled)**

3. **(Canceled)**

4. **(Currently amended)** ~~The isolated and~~ recombinant fusion peptabody of claim 1 ~~claims 1-3~~, wherein said ~~isolated and~~ recombinant fusion peptabody is multimeric.

5. **(Currently amended)** ~~The isolated and~~ recombinant fusion peptabody of claim 1 ~~claims 1-4~~, wherein the peptide enhancer sequence is selected from the group consisting of ~~comprising:~~ YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR.

6. **(Currently amended)** ~~The isolated and~~ recombinant fusion peptabody of claim 1, ~~claims 1-5~~, wherein said epidermal growth factor receptor ligand is selected from ~~among~~ the group consisting of:

- (a) an epidermal growth factor polypeptide or fragments or variants thereof,
- (b) a growth blocking peptide or fragments or variants thereof,
- (c) a TGF alpha polypeptide or fragments or variants thereof,
- (d) a plasmocyte spreading peptide or fragments or variants thereof,
- (e) a paralytic peptide or fragments or variants thereof,
- (f) a cardioactive peptide or fragments or variants thereof,
- (g) an amphiregulin polypeptide or fragments or variants thereof,
- (h) a heparin-binding epidermal growth factor-like polypeptide or fragments or variants thereof,
- (i) a betacellulin polypeptide or fragments or variants thereof, and ~~or~~
- (j) a viral EGF-like polypeptide or fragments or variants thereof.

7. **(Currently amended)** The ~~isolated and~~ recombinant fusion peptabody of claim 6, wherein said epidermal growth factor receptor ligand is present in its full-length sequences.

8. **(Currently amended)** The ~~isolated and~~ recombinant fusion peptabody of claim 1 ~~claims 1-7~~, further comprising a polyhistidine tag sequence.

9. **(Currently amended)** The ~~isolated and~~ recombinant fusion peptabody of claim 1, ~~claims 1-8~~, further comprising at least one effector region.

10. **(Currently amended)** The ~~isolated and~~ recombinant fusion peptabody of claim 9, wherein the effector region comprises a cytotoxin or a detection moiety.

11. **(Canceled)**

12. **(Currently amended)** The ~~isolated and~~ recombinant fusion peptabody of claim 10 ~~11~~, wherein said detection moiety is fluorescent.

13. **(Currently amended)** An isolated nucleic acid comprising a ~~and purified~~ DNA sequence encoding the ~~isolated and~~ recombinant fusion peptabody of claim 1 ~~any one of claims 1-9~~.

14. **(Currently amended)** A vector comprising at least one copy of the isolated nucleic acid ~~isolated and purified DNA sequence~~ of claim 13.
15. **(Currently amended)** The vector of claim 14, further comprising a promoter operably linked to said isolated nucleic acid ~~and purified DNA molecule~~.
16. **(Currently amended)** A prokaryotic or eukaryotic host cell capable of expressing the isolated nucleic acid ~~and purified DNA molecule~~ of claim 13.
17. **(Currently amended)** A pharmaceutical composition comprising ~~as an active substance a pharmaceutically effective amount of an isolated and~~ the recombinant fusion peptabody of claim 1, claims 1-12 optionally in combination with and a pharmaceutically acceptable carrier, carriers, diluents and adjuvants.
18. **(Canceled)**
19. **(Canceled)**
20. **(Canceled)**
21. **(Currently amended)** A method of treating or preventing cancer characterized by expression of an ~~that expresses~~ epidermal growth factor receptors selected from the group consisting of ErbB1, ErbB3, and ErbB4, comprising administering the pharmaceutical composition of claim 17 to a subject, wherein the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, liposarcoma, neuroendocrine tumor, mesothelioma, schwannoma, meningioma, adenocarcinoma, melanoma, leukemia, lymphoid malignancy, squamous cell cancer, epithelial squamous cell cancer, lung cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine

carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, a tumor of the biliary tract, and head cancer, and neck cancer, ~~comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 17 to a subject.~~

22. (Canceled)

23. (Currently amended) A method for inducing apoptosis and/or necrosis, comprising contacting a cell with the ~~isolated and~~ recombinant fusion peptabody of claim 1 ~~claims 1-12.~~

24. (Original) The method of claim 23, wherein said cell is a cancer cell.

25. (Currently amended) A method for inhibiting cell proliferation, comprising contacting a cell with the ~~isolated and~~ recombinant fusion peptabody of claim 1 ~~claims 1-12.~~

26. (Original) The method of claim 25, wherein said cell is a cancer cell.

27. (Currently amended) A method of diagnosing cancer comprising administering to a subject the ~~isolated and~~ recombinant fusion peptabody of claim 10, ~~claims 11-12, optionally in combination with pharmaceutically acceptable carriers, diluents and adjuvants.~~

28. (Currently amended) A kit for treating cancer characterized by expression of an ~~that expresses~~ epidermal growth factor receptors selected from the group consisting of ErbB1, ErbB3, and ErbB4, in a human patient, said kit comprising the ~~isolated and~~ recombinant fusion peptabody of claim 1 ~~claims 1-12, optionally with reagents and/or instructions for use administering the recombinant fusion peptabody to the human patient for the treatment of~~ cancer.

29. (Currently amended) The kit of claim 28, further comprising a separate pharmaceutical dosage form comprising an additional anti-cancer agent selected from the group

consisting of a chemotherapeutic agents, an anti-epidermal growth factor receptors antibody antibodies, a radioimmunotherapeutic agents, and combinations thereof.

30. **(Currently amended)** A kit for diagnosing cancer characterized by expression of an that expresses epidermal growth factor receptors selected from the group consisting of ErbB1, ErbB3, and ErbB4, in a human patient, said kit comprising the ~~isolated and~~ recombinant fusion peptabody of claim 10, ~~claims 11-12, optionally with reagents and/or instructions for use.~~

31. **(Currently amended)** A method for producing the ~~isolated and~~ recombinant fusion peptabody of claim 1 ~~claims 1-12~~, comprising ~~the steps of:~~

- a) constructing a ~~an isolated and purified~~ DNA molecule encoding the ~~isolated and~~ recombinant fusion peptabody of claim 1 ~~any one of claims 1-12~~;
- b) allowing expression of said ~~isolated and purified~~ DNA molecule in a cell expression system under suitable conditions; and
- c) recovering the ~~isolated and~~ recombinant fusion peptabody.

32. **(Original)** The method of claim 31, characterized in that the cell expression system is a prokaryotic cell.

33. **(Currently amended)** The method of claim 31 ~~claims 31-32~~, characterized in that the suitable conditions comprise ~~consist in~~ culturing the cell expression system at a temperature between 10-40 °C during 2-40 hours.

34. **(Currently amended)** The method of claim 33, characterized in that the suitable conditions comprise culturing the cell expression system at ~~consist in~~ a temperature of 37°C during 8-16 hours.

35. **(Currently amended)** The method of claim 31 ~~claims 31-34~~, characterized in that step c) is achieved by extraction of said ~~isolated and~~ recombinant fusion peptabody from the cell expression system subsequently followed by purification and refolding steps.

36. **(Original)** The method of claim 35, characterized in that the purification is carried out in the presence of reducing agents and results in the elimination of contamination.

37. **(Original)** The method of claim 35, characterized in that the refolding step is carried out by direct dilution in refolding buffer and further comprises serial dialysis.

38. **(Currently amended)** The method of claim 37, further characterized by at least one of the following conditions:

- a) ~~in that~~ the direct dilution in refolding buffer leads to a final concentration of the ~~isolated and~~ recombinant fusion peptabody below 300 nM;
- b) the serial dialysis comprise at least 2 different dialysis buffers; or
- c) the refolding step consists in the oxidation of the recombinant fusion peptabody before its concentration.

39. **(Canceled)**

40. **(Canceled)**

41. **(Currently amended)** An ~~purified and isolated~~ peptide enhancer sequence comprising an amino acid sequence having protein production increasing activity, characterized in that said ~~purified and isolated enhancer sequence~~ is selected from the group consisting of ~~comprising~~ YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR, a molecular chimera thereof, and variants thereof.

42. (New) A recombinant protein comprising the enhancer peptide of claim 41.

43. (New) A recombinant fusion peptabody, which binds to the epidermal growth factor receptor ErbB-1 comprising:

- (a) a portion of a cartilage oligomer matrix polypeptide;
- (b) a peptide enhancer sequence for increasing protein production, located at the N terminus of the portion of the cartilage oligomer matrix polypeptide and having a sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR;
- (c) a portion of a hinge region of an immunoglobulin polypeptide located at the C terminus of the portion of the cartilage oligomer matrix polypeptide; and
- (d) an epidermal growth factor receptor ligand located at the C terminus of the hinge region,

wherein said recombinant fusion peptabody is capable of inducing cellular death in a cell expressing the epidermal growth factor receptor.

44. (New) A monomer of a peptabody comprising

- (a) a portion of a cartilage oligomer matrix polypeptide;
- (b) an enhancer peptide sequence located at the N terminus of the portion of the cartilage oligomer matrix polypeptide;
- (c) a portion of a hinge region of an immunoglobulin polypeptide located at the C terminus of the portion of the cartilage oligomer matrix polypeptide; and
- (d) an epidermal growth factor receptor ligand located at the C terminus of the hinge region, wherein the epidermal growth factor receptor ligand binds to an epidermal growth factor receptor selected from the group consisting of ErbB-1, ErbB-3 or ErbB-4.

45. (New) The monomer of claim 44, wherein said monomer forms a multimeric molecule.

46. (New) The monomer of claim 45, wherein the multimeric molecule is pentameric or decameric.

47. (New) The monomer of 44, wherein the enhancer peptide sequence is selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, YSFEDLYRR, and variants thereof.

48. (New) An isolated nucleic acid comprising a DNA sequence encoding the monomer of claim 44.

49. (New) An isolated and recombinant fusion peptabody, which binds to an epidermal growth factor receptor selected from the group consisting of ErbB-1, ErbB-3, and ErbB-4, comprising:

- (a) a portion of a humanized or human cartilage oligomer matrix polypeptide;
- (b) a peptide enhancer sequence for increasing protein production located at the N terminus of the portion of the cartilage oligomer matrix polypeptide;
- (c) a portion of a hinge region of an immunoglobulin polypeptide located at the C terminus of the portion of the cartilage oligomer matrix polypeptide; and
- (d) an epidermal growth factor receptor ligand located at the C terminus of the hinge region,

wherein said isolated and recombinant fusion peptabody is capable of inducing cellular death in a cell expressing said epidermal growth factor receptor.